REMARKS

This application originally contains claims 1-50. Claims 1-50 have been cancelled without prejudice and new claims 51-80 have been added.

Support for claims 51-80 is found in the specification as follows:

"A combination of at least one polymer ... and at least one of ..." is supported in the specification on page 1, paragraph 2:

The present invention relates to compositions comprising bone marrow cells (BMC) and demineralized bone matrix (DBM), supplemented with a site-responsive polymer, and to their novel uses in induction of new bone and cartilage formation in mammals.

Support for bone marrow as a source of mesenchymal stem cells is found in the specification on page 1, paragraph 5 and page 15, paragraph 5:

It was shown that multipotent mesenchymal stem cells, which are capable of extensive proliferation and differentiation into cartilage, bone, tendon, muscle, fat and etc. are present in the bone marrow.

In a second aspect, said composition comprising BMC and DBM together with a site responsive polymer, is intended for use in transplantation of mesenchymal progenitor cells present in the bone marrow into a joint or a cranio-facial-maxillary area of a subject in need ...

Support for DBM as a source of bone morphogenic proteins or growth factors is found in the specification on page 2, paragraph 3:

DBM is also a natural source for Bone Morphogenic Proteins-growth factors that play an important role in the formation of bone and cartilage.

Support for use of DBM or demineralized tooth matrix (DTM) is found in the specification on page 15, paragraph 3:

The present invention relates to compositions comprising a mixture of bone marrow cells (BMC) and demineralized bone or tooth matrix (DBM or DTM, respectively), together with a site-responsive polymer and to their novel uses in the transplantation of mesenchymal progenitor cells into joints and cranio-facial-maxillary area (when the bone is absent to induce bone formation).

Support for "a polymer which will show a 2 fold increase in viscosity due to a triggering effect which can be temperature or pH" is found in the specification on page 23, paragraph 3 and the paragraph bridging pages 32-33:

According to the present invention, the most preferred RTG polymers to be employed comprise amphiphiles obtained by the combination of both hydrophobic and hydrophilic basic segments, which, separately, do not display any kind of clinically relevant viscosity change of their own, and are capable of undergoing a transition that results in a sharp increase in viscosity in response to a triggering effected at a predetermined body site and an aqueous-based solvent wherein the viscosity of said polymeric component increases by at least about 2 times upon exposure to a predetermined trigger.

The site-responsive polymer may be a reverse thermogelating (RTG) polymer, or a polymer which responses to triggers other than or additional to body temperature, for example, pH, ionic strength, etc. In a particular embodiment, the site-responsive polymer may be a polymeric system comprising at least one silicon-containing reactive group. Polymeric components of this system may be RTG polymers, or otherwise responsive polymers, or combinations thereof.

Support for "having a viscosity of at least 22,000 Pas" is found in example 23 of the incorporated U.S. patent application referenced in the specification on page 19, paragraph 4:

Particularly preferred are novel polymers which are the subject of co-pending United States Patent Application filed on August 15, 2002, entitled Novel Thermosensitive Block Copolymers for Non-Invasive Surgery, the contents of which are fully incorporated herein by reference.

- The modification of the PEG6000/PPG3000 in the synthesis step rendered different PEO/PPO ratios in the final poly(ether-carbonate). The following table exemplifies the different PEO/PPO ratios achieved as well as the rheological parameters in 15% aqueous solutions. Where T_i is the gelation temperature.

PEG [wt.%]	T_i [°C]	□37°C [Pa.s]
81	27	17,000
77	21	62,000
71	14	83,400
62	10	42,000

Support for "Molecular weight higher than 17,000 Daltons" is found in the specification on page 54, paragraph 5:

Polymer N7 Alternating[-PEG6000-O-CO-0-PPG3000-]$_n$ poly (ether-carbonate)..... The molecular weight of the polymer produced was Mn 36,400 as determined by GPC.

Support for "Having more than 3 blocks" is found in the specification on in the paragraph bridging pages 20-21:

More specifically, in one of the preferred embodiments, the RTG polymers applicable in the compositions and methods of the present invention are selected from the group consisting of polymers having the general formulae: (a)[-X_n-A-X_n-E-B-E-]$_m$ defined herein as formula Ia ; (b)[-X_n-B-X_n-E-A-E-]$_m$ defined herein as formula Ib; (c)M-X_n-E-B-E-X_n-M defined herein as formula IIa; (d)N-X_n-E-A-E-X_n-N defined herein as formula IIb ; (e)[-X_n-A(X_n)$_y$(E)$_y$(B)$_y$-X_n-E-B-E-]$_m$ defined herein as formula IIIa ; (f)[-X_n-B(X_n)$_y$(E)$_y$(A)$_y$-X_n-E-A- E-]$_m$ defined herein as formula IIIb; wherein A represents a bifunctional, trifunctional or multifunctional hydrophilic segment; M represents a monofunctional hydrophilic segment; B represents a bifunctional, trifunctional or multifunctional hydrophobic segment; N represents a monofunctional hydrophobic segment; X represents a bifunctional degradable segment; E represents bi, tri or multifunctional chain extender or coupler; n and m represent the respective degree of polymerization and y designates the additional functionality of the corresponding segment (wherein y > 2).

Support for "Capable of undergoing a condensation reaction in the presence of water resulting in an increase in the molecular weight of the polymeric system" is found in the specification on page 34, paragraph 3:

More specifically this polymeric system comprises one or more silicon-containing reactive groups capable of undergoing a condensation reaction primarily at a predetermined body site, in the presence of water and at body temperature, at an appropriate pH, wherein said reaction results in an increase in the molecular weight of the polymeric system due to polymerization and/or crosslinking and produces at least a partial change in the rheological and mechanical properties of said polymeric system.

Support for "having a polymer degradation time ..." is found in the specification on page 7, paragraph 3 and page 69, paragraph 2 and in Fig. 9, and the description thereof, of the incorporated U.S. patent application referenced in the specification on page 19, paragraph 4:

The supplement has to be slowly biodegradable or dissolvable in the body fluids, the degradation time being compatible with the period of de novo chondro- and osteogenesis.

However regenerating surface was built of connective tissue alone when BMC were accompanied by RTG polymers N2 or N4, while in the cases in which BMC were supplemented with RTG N7 regenerating surface of the damaged area comprised a mixture of connective tissue with cartilage cells.

Particularly preferred are novel polymers which are the subject of co-pending United States Patent Application filed on August 15, 2002), entitled Novel Thermosensitive Block Copolymers for Non-Invasive Surgery, the contents of which are fully incorporated herein by reference.

In the case of biodegradable systems, these materials are engineered to display different degradation kinetics. It is an additional object of the invention to introduce hydrolytically unstable segments along the polymeric backbone, allowing, therefore, to fine tune both the degradation rate of the polymer molecule as well as control the stability of the whole system and its rheological properties. FIG. 9 is a graphical representation of the degradation of poly(ether-carbonate), poly(ether-ester-carbonate) and poly(ether-ester) with time.

Support for "composition also comprising living cells selected from ..." (claim 66) is found in the specification on page 35, paragraph 2:

In further preferred embodiments the composition of the invention may comprise, in addition to the responsive polymeric system or polymer and the BMC and DBM, at least one additional biomolecule to be delivered into the body such as elastin, collagenous material, albumin, a fibrinous material, growth factors, enzymes, hormones, living cells such as endothelial cells, hepatocytes, astrocytes, osteoblasts, chondrocytes, fibroblasts, miocytes, and combinations thereof.

Support for "polymer ... is a segmented block copolymer ..." (claim 67) is found in the specification in the paragraph bridging pages 23-24, and on page 54, paragraph 5 and page 68, paragraph 4:

In further preferred embodiments of the present invention said responsive component is a segmented block copolymer comprising polyethylene oxide (PEO) and polypropylene oxide (PPO) chains, wherein said PEO and PPO chains are connected via a chain extender, wherein said chain extender is a bifunctional, trifunctional or multifunctional molecule selected from a group consisting of phosgene, aliphatic or aromatic dicarboxylic acids, their reactive derivatives such as acyl chlorides and anhydrides, diamines, diols,aminoacids, oligopeptides, polypeptides, or cyanuric chloride or any other bifunctional, trifunctional or multifunctional coupling agent, or other molecules, synthetic or of biological origin, able to react with the mono, bi, tri or multifunctional-OH,-SH,-COOH,-NH_2,-CN or-NCO group terminated hydrophobic and hydrophilic components or any other bifunctional or multifunctional segment, and/or combinations thereof.

Polymer N7 Alternating[-PEG6000-O-CO-0-PPG3000-]$_n$ poly (ether-carbonate)...

When DBM-BMC complex was transplanted into the damaged area accompanied by RTG polymer N7 regenerating surface was built of thick layer of young hyaline cartilage.

Support for the method recited in claim 68 is found in the specification on page 17, paragraph 2:

In a first embodiment of the method of the invention, the mixture is administered by any one of the following procedures injection, minimally invasive arthroscopic procedure, or by surgical arthroplasty into the site of implantation, wherein said method is for support or correction of congenital or acquired abnormalities of the joints, cranio-facial-maxillary bones, orthodontic procedures, bone or articular bone replacement following surgery, trauma or other congenital or acquired abnormalities, and for supporting other musculoskeletal implants, particularly artificial and synthetic implants.

Support for the method recited in claim 75 is found in the specification on page 47, paragraphs 2-3:

3. Preparing a composition comprising a suspension of BMC, at a cell concentration ranging from $1x10^6$/ml to $4x10^{10}$/ml and mixing it with DBM at a ratio of from 1:1 to 20:1, preferably between 2:1 to 9:1, most preferably the composition of the invention is at a ratio of 4 parts BMC concentrate to 1 part of DBM in powder form (volume:volume). MBM may be used instead of DBM. If so desired, BMP may optionally be included in the composition.

4. Adding to the composition obtained in step 3 a site-responsive polymer, at an optimal concentration for the site-responsive polymer used.

Favorable consideration of the amended claims is respectfully requested.

Respectfully submitted,

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